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Access to prescribing information for paediatric medicines in the USA: post-modernization

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Children have reduced access to medicines because of inadequate prescribing information and paucity of suitable formulations.
- The USA has implemented a series of measures designed to improve the licensing of medicines for children, which has resulted in an increase in the number of studies and the number of patients studied in investigational trials of medicines in children.
- These measures have increased the number of targeted medicines that have had their labelled use extended to children.

WHAT THIS STUDY ADDS

- Information in the Physicians' Desk Reference did not indicate that there was an improvement in overall access to, and prescribing information about, drugs in the paediatric population in the USA over the time period 1998–2007.

AIMS

The aims of the present study were to examine the Physicians' Desk Reference (PDR) for changes in the listing of medicines licensed for children in the USA over a 10-year period (1998–2007).

METHODS

The USA PDR was used to identify products listed in 1998, 2002 and 2007. Information about generic name (active agent), salt, strength, brand name, suitability of formulation, paediatric licensing information and the lowest age of licensing was extracted. Prescription products were collapsed down to chemical entities/fixed-dose combinations.

RESULTS

Of the prescription entities listed in the PDR, 538 (55.9%), 488 (54.3%) and 394 (51.3%) were licensed for children in 1998, 2002 and 2007, respectively. There was a 39% decrease in the number of entities licensed for the newborn and a 34% decrease for children aged 2–6 years between 1998 and 2007. Formulations suitable for children were listed for 611 (63.4%), 550 (61.2%) and 430 (60.6%), respectively. Prescription entities with both a suitable oral formulation and licensing for children numbered 161 (16.7%), 148 (16.5%) and 100 (14.1%) in 1998, 2002 and 2007, respectively.

CONCLUSIONS

The listings in the PDR suggest that overall access to prescribing information about drugs in the paediatric population has not shown an increase over the decade. This particularly affected the neonatal age group.

The USA has been at the forefront of a move to improve the licensing of medicines for children and has made several regulatory and legislative moves to this effect. The Best Pharmaceuticals for Children Act (BPCA) was established in January 2002 to replace the Food and Drug Administration Modernisation Act, which expired in 2001 [1]. The BPCA offers a 6-month patent extension in exchange for the submission of new paediatric data following a written request by the Food and Drug Administration (FDA) (Pediatric Exclusivity Provision). In addition, Congress established the Pediatric Research Equity Act (PREA) in 2003, which requires paediatric trials to be performed for drugs that

have potential for paediatric use [2]. This applies to both new drugs and those already approved. The PREA is a renewal of the Final Pediatric Rule, which was overturned in 2002. Both the BPCA and PREA were re-authorized in 2007. Re-authorization has resulted in increased authority to refer and require studies under PREA; increased authority and effectiveness for BPCA improvements: and increased transparency of programmes and dissemination of paediatric information [3]. The European Union has enacted similar initiatives [4]. However, it is not yet clear how successful the USA initiatives have been in increasing the number of medicines specific to children and increasing prescribing information.

There is evidence that the strategies in the USA are having limited success. Of the 133 new medical entities approved in the USA from 1998 to 2002, the number licensed for children increased from five (4%) to 39 (29%) over the 3 years from initial registration [5]. Furthermore, 79 (59%) drugs were in suitable formulations for children and 27 (20%) were both licensed and suitably formulated for children. The paediatric exclusivity programme has encouraged studies of drugs in children, as evidenced by 253 studies submitted to the FDA between 1998 and 2004 [6]. However, of the 79 medicines granted a patent extension as of 10 November 2003, 58 had attained paediatric licensing, 45 were licensed for children aged <12 years, 35 for <6 years, 19 for <2 years and six for <1 month [7]. These data suggested that paediatric exclusivity was delivering benefits for older children, but not for younger children. In addition, the return to the drug sponsor is highly variable, with an estimated net return-to-cost ratio ranging from −0.68 to 73.63, representing a net return ranging from a loss of $US9 million to a gain of $US508 million [8].

Access to medicines involves presentation (formulation) and affordability in addition to licensing [9–11]. Although a medicine may be licensed for children, it may not be in a suitable formulation, and this becomes a barrier to access [12]. It is essential that medicines are in an appropriate formulation for children, as the majority of this population, especially infants and younger children, have difficulty swallowing tablets and capsules. Families with young children may be disadvantaged financially, and the availability of subsidized medicines and cheaper generics becomes a major issue. Recent US legislation is attempting to rectify this deficiency in child-friendly formulations. The BPCA 2007 requires paediatric studies to be undertaken in a suitable formulation for the age group being studied with a proviso that manufacturers can decline if they are unable to produce a paediatric formulation. However, in the latter case, the legislation requires the manufacturer to submit to the FDA the reasons why the formulation cannot be developed [13]. Furthermore, BPCA 2007 'requires prominent public disclosure when a manufacturer creates a pediatric formulation and fails to market it' and requires the FDA to monitor the number of paediatric formulations developed or not developed, and the reasons for them not being developed [13].

The aims of the present study were to examine the Physicians' Desk Reference (PDR) for changes in the listing of medicines licensed for children in the USA over a 10-year period (1998–2007) and to determine changes in the numbers and proportions of suitable formulations of those medicines.

Methods

All products listed in the 1998, 2002 and 2007 USA PDR were identified and examined to extract the following information: generic name (active agent), salt, strength, brand name, suitability of formulation, paediatric licensing information and the lowest age the medicine was licensed for [14–16]. Hard-copy versions of the PDR were examined for each year 1998 and 2002, and 2007. Products lacking information regarding paediatric licensing were assumed to have no paediatric indications. Products lacking dose and prescribing information (listed with generic and brand names, strength and formulation only) were excluded from data analysis. If a product contained information on paediatric dosing by body weight instead of age, the equivalent lowest age licensed for was extrapolated using the British National Formulary [17].

The products were divided into the following categories based on their route of administration: suitable oral, i.e. liquid, powder, oral spray, soluble tablets and chewable tablets; unsuitable oral, i.e. tablets, caplets, capsules and other solid preparations; injectable, i.e. infusions, intravenous and intramuscular injections; ears/eyes, i.e. ophthalmic solutions and aural ointments; nasal, i.e. topical or aerosolized nasal medications; dermal, i.e. medicines applied topically, including transdermal patches; rectal, i.e. enemas and suppositories; vaginal, i.e. pessaries and vaginal inserts; inhalation/inhalers; and other, i.e. miscellaneous preparations that did not fall under the above categories. All products that were not classed as unsuitable oral were also categorized as suitable for children, i.e. formulations that can be administered to a child.

Paediatric age groups were adapted from the International Conference on Harmonisation's classification: term newborn infants (0–27 days), infants/toddlers (28 days to 23 months), children (2–11 years) and adolescents (12–16/18 years) [18]. The 2–11 age group was subdivided into two further categories (2–6 years and 7–11 years) to provide a more detailed analysis. The lowest age category of licensing was determined and categorized as: newborns, infants/toddlers, 2–6 years, 7–11 years and 12–18 years.

The products were collapsed down to entities (chemical entities/fixed-dose combinations, i.e. medicines classified according to their generic composition) that were only available on prescription using STATA Version 8 (STATA

Corp., College Station, TX, USA). The main unit for analysis was therefore 'prescription entities'. Classifications were made on the basis of 'best case' (i.e. if any formulation was licensed for children then the entity was classified as being licensed for children). These data were then analysed to determine the paediatric licensing status and suitability for children according to year, type of formulation and age group. Prescription entities newly listed by 2002 and 2007 were identified and categorized using the World Health Organization's Anatomic Therapeutic Chemical classification (ATC) [19]. Entities no longer listed in 2007 and their former paediatric licensing status were identified. A theoretical paediatric licensing status for 2007 was calculated by adding the entities no longer listed in 2007 to those listed.

Results

Over 2000 products with full prescribing information were listed in each PDR: 2577 (1998), 2139 (2002) and 2894 (2007). After collapsing the data, <1000 prescription entities were listed each year, and numbers decreased by 2007 (Table 1). Over 50% of prescription entities listed in respective years were licensed for children, and numbers and proportions licensed for children decreased by the year 2007. In 2007, 684 prescription entities were no longer listed in the PDR, and 327 of these were known to be licensed for children. When adjusted for entities no longer listed in the PDR, 691 of 1394 prescription entities in 2007 could theoretically have been licensed for children (49.6%; Table 2).

The numbers of prescription entities listed that were in suitable formulations for children decreased by 2007, but the proportions remained similar over the decade (Table 1). The number of prescription entities listed in a suitable oral formulation for children decreased by 2007 and the proportion decreased slightly. The three main formulation types throughout the period comprised: unsuitable oral (>57%), injectable (>38%) and suitable oral (>17%). The numbers of every formulation type decreased over time, but the proportions of different formulation types remained similar over the decade. The numbers and proportions of prescription entities listed that were licensed and in suitable formulations for children decreased by 2007, as did numbers licensed and in suitable oral formulations.

Over the decade, the number of prescription entities listed in each PDR that were licensed for children decreased by about one-third. Most notable was a 39% decrease in the number of entities for the newborn and a 34% decrease in entities for children aged 2–6 years (Table 3). The proportion of prescription entities licensed for children for each age group showed little change throughout the period. The proportion of all prescription entities for the newborn and children 2–6 years old decreased more notably than other categories.

Table 1

Prescription entities in the Physicians' Desk Reference: licensing status and suitability for children

	1998		2002		2007	
Prescription entities	963		899		710	
Licensed for children	538	55.9%	488	54.3%	364	51.3%
Suitable formulation for children	611	63.4%	550	61.2%	430	60.6%
Suitable oral formulation for children	199	20.7%	183	20.4%	124	17.5%
Unsuitable oral formulation	550	57.1%	541	60.2%	413	58.2%
Suitable formulation and licensed for children	387	40.2%	352	39.2%	256	36.1%
Suitable oral formulation and licensed for children	161	16.7%	148	16.5%	100	14.1%

Table 3

Prescription entities: lowest age licensed

	1998			2002			2007		
Age group	***n***	**%***	**%†**	***n***	**%***	**%†**	***n***	**%***	**%†**
Newborn	191	35.4	19.8	164	33.5	18.5	116	32.0	16.3
Infants	110	20.4	11.4	105	21.5	11.7	82	22.6	11.5
2–6 years	115	21.3	11.6	109	22.3	12.1	76	20.9	10.7
7–11 years	20	3.7	2.1	15	3.1	1.7	17	4.7	2.4
12–18 years	103	19.1	10.7	96	19.6	10.7	72	19.8	10.1

*Prescription entities licensed for children. †All prescription entities.

Table 2

Prescription entities in the Physicians' Desk Reference (PDR) 2007: licensing status adjusted for entities no longer listed

	Listed in PDR 2007 (x)	No longer listed in PDR 2007 (y)	Theoretical licensing status by 2007* (x + y)
Prescription entities	710	684	1394
Licensed for children	364	327	691
Percentage of prescription entities licensed for children	51.3%	47.8%	49.6%

*Theoretical licensing status includes entities both listed and no longer listed by 2007.

Table 4

Prescription entities: newly listed and licensed by 2002 and 2007

	1998–2002		2003–2007	
Newly licensed prescription entities	248		212	
Licensed for children	106	42.7%	72	34.0%
Suitable form for children	149	60.1%	122	57.5%
Licensed, suitable formulations for children	77	31.0%	55	25.8%
Suitable oral formulations	29	11.7%	11	5.2%
Licensed, suitable oral formulations for children	21	8.5%	7	3.3%

Table 5

Proportion of newly listed prescription entities by Anatomic Therapeutic Chemical (ATC) category, 2002 and 2007

ATC categories		2002		2007	
Alimentary tract and metabolism	A	35	14.1%	30	14.2%
Blood and blood forming organs	B	17	6.9%	11	5.2%
Cardiovascular system	C	23	9.3%	23	10.8%
Dermal	D	13	5.2%	7	3.3%
Genitourinary	H	20	8.1%	16	7.5%
Systemic hormonal preparations excluding sex hormones and insulin	G	6	2.4%	7	3.3%
Anti-infectives for systemic use	J	30	12.1%	36	17.0%
Antineoplastic and immunomodulating agents	L	29	11.7%	29	13.7%
Musculoskeletal system	M	9	3.6%	9	4.2%
Nervous system	N	34	13.7%	25	11.8%
Antiparasitic products	P	1	0.4%	2	0.9%
Respiratory system	R	18	7.3%	5	2.4
Sensory system	S	10	4.0%	3	1.4%
Various	V	3	1.2%	9	4.2%
All		248	100%	212	100%

A total of 248 prescription entities were newly listed in the 2002 PDR and 212 in the 2007 PDR (Table 4). Of those newly listed, 106 (43%) and 72 (34%) were licensed for children. The proportion of newly listed entities licensed for children was smaller than the proportion of all prescription entities licensed for children in each of the years examined. The number in a suitable formulation for children decreased in the second 5-year period, as did the number that were licensed for children and in suitable forms. By the second period, there was a decreased number, and proportion, of oral formulations suitable for children and licensed and in suitable oral formulations.

Analysis by ATC category found a small increase in numbers and proportions of systemic anti-infective agents in 2007 compared with 2002 and a small increase in the proportion of antineoplastic agents and cardiovascular agents (Table 5). The most commonly newly listed entities in both years were agents for: the alimentary tract and metabolism, nervous system, cardiovascular system, systemic infections, and antineoplastic and immunomodulating agents. Entities in these groups accounted for 60% of newly listed entities in 2002, and 68% in 2007.

Discussion

Over the 10-year period from 1998 to 2007 there was an overall decrease in the number of prescription entities listed in the PDR and a decrease in both the number and proportion licensed for children. In the PDR listings, there was a decrease in the numbers and proportions of prescription entities with a suitable formulation for children, in those with a suitable oral formulation, and in those licensed and suitably formulated for children. There was an increase in paediatric licensing of anti-infective and antineoplastic agents that would be of particular benefit to the paediatric age group. There was a slight increase in the proportion of prescription entities licensed for the 2–6 and 7–11 age groups, but a decrease in the number and proportion licensed for newborns. It is not clear whether this represents a failure of policies to improve the licensing of medicines for children, a decrease in listing of medicines in the PDR, an overall reduction in medicines marketed in the USA or a rationalization of drug use in children.

International comparisons with the USA are difficult to make. Changes in paediatric licensing to some extent may represent 'catch-up' with the USA, and the pharmaceutical markets differ in the use of generic in comparison with innovator medicines. Over the time period 1998–2002 there was an increase in the total number of chemical entities registered in the UK, with small increases in the proportion licensed for children and in the availability of suitable paediatric formulations [9]. In Australia, over the same time period, there was an increase in the licensing of medicines for children, but this was from a low baseline in 1998 [11]. In New Zealand, over the same time period, there was a reduction in the number of orally available chemical entities, including those licensed for children, but all of the medicines withdrawn from the market had therapeutic alternatives [10].

The PDR is a voluntary listing of medicines, and also incurs a fee for listing. Over the decade many medicines have become only available in generic form, and manufacturers of generic medicines might be deterred from listing in the PDR, or restrict the size of their entry, because of the fee. Over a third (1634/4207) and almost half (1737/3801) of the products in the 1998 and 2002 PDR, respectively, were excluded from analysis due to lack of prescribing information. The prescription entities listed in the PDR that had no paediatric licensing information were assumed to have no paediatric indications (i.e. were not licensed for children), but it is possible that such information was omitted in order to limit the size of the entry. However, such information would be useful in situations where

off-label or unlicensed use of the medication in children is necessary.

The pharmaceutical industry has undergone a process of rationalizing, with the possible consequence of a reduction in the number of prescription entities available in the USA. A possible reason for this could be the merging of pharmaceutical companies. Pharmaceutical companies may merge because of the high costs of research and development and the fact that combining their financial and marketing resources may enable them to cover advertising costs sufficiently and respond to promotional demands [20]. Glaxo SmithKline provide an example of this, as the $US76 billion proposed merger between Glaxo Wellcome and SmithKline Beecham was expected to gain the combined company 7.3% of the global market share and a $US4.7 billion budget for research and development. As a consequence of merging, pharmaceutical companies may withdraw older drugs that have been on the market for some time in the hope that a reduced number of new innovator drugs will replace them. This decrease in prescription entities may also be due to pharmaceutical companies withdrawing drugs that are not as widely used as before. Also, new drugs are becoming increasingly more difficult to discover. This is illustrated by a decrease in the percentage of drugs in preclinical trials that are ultimately launched—between 1995 and 2000 the proportion was approximately 12.5%, but dropped in 2004 to <8% [20].

Another possible reason for withdrawal of drugs is because of adverse drug reactions (ADRs) found some time after they have been on the market, e.g. Vioxx (rofecoxib), which was approved by the FDA in 1999 [21]. Originally hailed as a blockbuster drug, 5 years later the association between Vioxx and an increased risk of serious thrombotic cardiovascular events prompted Merck & Co. to withdraw the drug voluntarily [22, 23]. Other drug companies may be hesitant to produce generics or innovate different drugs in the same class (e.g. COX-2 inhibitors) due to an increased possibility of serious ADRs—it would be a financial risk that many pharmaceutical companies may not be willing to take. Also, even if the new innovator drug (from the same class as the withdrawn drug) was found not to have serious side-effects, it may still be some time before the negative reputation of the class in the eyes of health practitioners and the public alike can be reversed.

There may have been a rationalization of drug use in paediatrics as a result of the knowledge gained through the paediatric licensing initiatives. A change in paediatric licensing of certain drugs could have occurred because ADRs were discovered, or the drug was found to be inefficacious in children. For example, the lowest licensing age for Lotrisone™ (betamethasone and clotrimazole, a treatment for symptomatic inflammatory tinea pedis, tinea cruris and tinea corporis) was increased from 12 to 17 years after further paediatric studies were carried out [24]. These studies demonstrated adrenal suppression not previously documented in patients <17 years old. Furthermore, although a medicine may be granted paediatric exclusivity, this is completely independent of whether the medicine will obtain licensing for paediatric use or not. Of the 79 medicines granted 'paediatric exclusivity' in the USA (up to 10 November 2003), only 58 (73%) were licensed for paediatric use [7].

The present study has shown that the percentage of prescription entities indicated for use in neonates decreased 9% over the 10-year period. This change was balanced by increased proportions of prescription entities licensed for use in older age groups, especially in those aged 2–6 and 7–11 years. As the BPCA does not offer greater incentives for paediatric data for younger compared with older children (i.e. it is a 'flat-rate' incentive), it is conceivable that the increased percentage of drugs licensed for use in older children may be due to the fact that it is potentially easier for pharmaceutical companies to recruit participants and conduct clinical trials in older children than in neonates. These findings are similar to those of an earlier study, which found improvements in licensing of medicines for children >6 years old but not for younger age groups, subsequent to the Pediatric Exclusivity Provision [7]. The incentives for paediatric licensing may be proving to be a 'blunt instrument', with inequities both in the return to the sponsor for conducting paediatric clinical trials, and the return to subgroups of the paediatric population, such as neonates.

There are several limitations to this study. First, many of the products in the hard-copy versions of the PDR lacked prescribing information and consequently had to be excluded from analysis. This may have affected the results by underestimating the total number of prescription entities, providing that they were unique prescription entities in these years, and inaccurately estimating those licensed for children. Another limitation is that not every single medicine available in the USA is listed in the PDR. It is up to the discretion of the pharmaceutical companies if, and how much, information is printed in the PDR. However, listing in the PDR is important because if a drug does not appear in the PDR, prescribers may not even be aware that it exists as a treatment option.

Conclusion

Despite the paediatric licensing initiatives overall, access to prescribing information about drugs in the paediatric population has not shown an increase over the decade. The incentives may need to be redirected at specific goals.

Competing interests

None declared.

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